REMARKS

I. Status of Claims

Claim 1 is amended to incorporate the subject matter of claims 7 and 8.

Claims 7 and 8 are canceled without prejudice or disclaimer.

No new matter is added. Accordingly, Applicants respectfully request entry and consideration of the Amendment. Upon entry of the Amendment, claims 1, 5 and 6 will be pending.

II. Response to Objection to the Specification

The Examiner has objected to the disclosure of the specification, because the disclosure does not possess a detailed description of the drawings.

The specification is amended to insert a description of the drawings, obviating the objection to the specification. Accordingly, Applicants respectfully request reconsideration and withdrawal of the objection.

III. Response to Claim Rejections Under 35 U.S.C. § 103(a)

A. Claims 1 and 5-8 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Takada et al. (U.S. Patent No. 6,117,455) in view of Jabes et al. ("Effectiveness of Rifabutin Alone or in Combination with Isoniazid in Preventive Therapy of Mouse Tuberculosis", *Antimicrobial Agents and Chemotherapy*, Vol. 38, No. 10, pp. 2346-2350 (1994)).

B. Claims 1 and 5-8 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Barrow et al. (U.S. Patent No. 6,264,991) in view of Jabes.

C. Claims 1 and 5-8 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Quenelle et al. (Antimicrobial Agents and Chemotherapy, 2001) in view of Jabes and Sharma et al. (Pharmaceutical Research, 2001).

Applicants respectfully traverse the above-identified § 103(a) rejections, at least for the following reasons.

Applicants submit that in order to establish a *prima facie* case of obviousness the prior art reference (or references when combined) must teach or suggest all of the claim limitations. *See* MPEP § 2142; *see also Velander v. Garner*, 348 F.3d 1359, 1363 (Fed. Cir. 2003). As established in *Graham v. John Deere Co.*, 383 U.S. 1 (1966), four factors control an obviousness inquiry – 1) scope and content of the prior art, 2) differences between the prior art and the claims, 3) level of ordinary skill in the pertinent art, and 4) objective evidence of non obviousness. *See Graham*, 383 U.S. at 17-18; *see also KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1734 (2007) (quoting *Graham*, 383 U.S. at 17-18). Moreover, a prior art reference must be considered in its entirety, i.e., as a **whole**, including portions that would lead away from the claimed invention. *See W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). A prior art reference teaches away when "a person of ordinary skill in the art, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *See In re Gurley*, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994); *Cf. Baxter International, Inc. v. McGraw, Inc.*, 149 F.3d 1321 (Fed. Cir. 1998).

Present claim 1 is drawn to a biodegradable inhalable microparticle composition useful for target specific drug delivery to manage pulmonary tuberculosis. The biodegradable inhalable microparticle composition consists of the anti-tubercular drugs rifabutin and isoniazid, and a biodegradable polymer for drug delivery wherein the ratio of drug(s): polymer is from about 1:2 to 2:1, and wherein the ratio of rifabutin to isoniazid is about 1:2 to 2:1. The size of the microparticles is between 1-15 microns in size, with at least 90% of the microparticles being less than 10 microns in size.

The ratio of rifabutin to isoniazid of 1:2.5 disclosed in Jabes does not fall within the currently claimed ratio of rifabutin to isoniazid. In Jabes, 1 part of rifabutin is used with 2.5 parts of isoniazid, whereas in present claim 1, 1 part of rifabutin is used with 2 parts of isoniazid, while 2 parts of rifabutin is used with 1 part of isoniazid, i.e., the ratio is about 1:2 to 1:0.5. Therefore, the presently claimed ratio of rifabutin to isoniazid is outside the scope of the Jabes' disclosure. Jabes limits the amount of rifabutin to 0.4 parts of isoniazid, i.e., rifabutin is always less than isoniazid, and teaches that the amount of isoniazid is more than 2.5 times greater than the amount of rifabutin. Hence, Jabes teaches away from the findings of the present inventors that it is possible to even have isoniazid present at half the amount of rifabutin (or rifabutin at twice the amount of isoniazid) together with increased efficacy. This finding of the presently claimed ratio of rifabutin to isoniazid being 1:2 to 2:1 is against the teaching of Jabes. Thus, one of ordinary skill in the art would not have been able to arrive at the findings of the present invention.

Furthermore, none of Jabes, Takada, Barrow or Quenelle teaches or suggests the drug to polymer ratio of present claim 1.

Sharma teaches a drug to polymer ratio of 1:3, whereas present claim 1 recites a drug: polymer ratio from 1:2 to 2:1. Thus, in Sharma 3 parts of polymer are used for every 1 part of drug, whereas in present claim 1, 2 parts of polymer are use for every 1 part of total drug and 1 part of polymer is used for every 2 parts of total drug. Therefore, Sharma limits the amount of drug to 0.33 parts of polymer, i.e., the amount of total drug is always less than the amount of polymer, and the amount of polymer is always greater than the amount of total drug, up to 3 times more. Thus, Sharma teaches away from the presently claimed invention which provides for the use of polymer in half the amount of total drug (or total drug at twice the amount of polymer) together with increased efficacy. This finding of drug: polymer ratio is contrary to the teaching of Sharma. Thus, one of ordinary skill in the art would not have been able to arrive at the findings of the present invention.

Moreover, a higher concentration of polymers – approximately three times that of total drug, as in the case of a Sharma, reduces the dosage of an active component, thereby reducing the bioavailability of the composition, and the efficiency of treatment of pulmonary tuberculosis. Thus, the claimed ratio of preparations/polymer is of substantive importance for the extended action of drugs in the lungs, because it provides greater bioavailability of the drug composition, and at the same time reduces the cost of treatment due to administration of the most favourable amount of polymer along with improved efficacy and reduced course of treatment. These advantages are supported by the experimental data in the last three paragraphs on page 11, and Figs. 1 and 2 of the specification.

Additionally, the Examiner acknowledges that Takeda teaches that there is a particle size difference between microparticles and microcapsules. Takeda discloses that the average diameter of the microcapsules is in the range of 0.5-400 μm, and more preferably 2-200 μm. The average diameter disclosed in Takeda is very broad. Present claim 1 recites microparticles which are 1-15 microns in size, where at least 90% of the microparticles are less than 10 microns in size. The size range of present claim 1 is very selective for enhanced efficacy of the present invention.

The present application is drawn to a combination of two anti-tubercular drugs which prevents the formation of adduct. The "consisting of" language of claim 1 excludes the use of rifampicin-type anti-tubercular drugs, which contain a piperazine moiety that can be attacked by isoniazid leading to the formation of an adduct which results in reduced bio-availability and efficacy of these drugs. The formation of adduct prevents the drug-combination from being used for management of pulmonary tuberculosis. See, for example, the paragraph just above the section titled "Materials and Methods" at page 1405, and the second paragraph in the section titled "Results and Discussion" at page 1407 of Sharma. The inventors found that the combination of drugs if used outside the claimed ratio, does not provide the intended benefit, i.e., the prevention of an adduct formation between the two drugs. Thus, the limitations of adduct formation have been overcome by the inventors in the instant application, and the presently claimed invention is economical as compared to conventional anti-tubercular compositions.

Further as discussed at page 11, lines 15-20 of the specification, the present application allows for the reduction of the number of drugs used in the effective treatment of tuberculosis from rifampicin, isoniazid, ethambutol and pyrazinamide to a combination of only rifabutin and isoniazid. The *in vivo* efficacy data of the combination as disclosed in the present application over pure drugs is shown in Figs. 1 and 2 of the specification, which provides further support for the unexpectedly superior properties of the presently claimed invention.

Applicants further submit that the composition of present claim 1 is distinguishable from that of the cited prior art, because it is designed specifically for the treatment of pulmonary tuberculosis, i.e. for the local delivery of a drug to a target, namely into the lungs. Moreover, as discussed above, the claimed composition does not contain rifampicin that is able to form complex compounds with isoniazid and includes a composition which, as established during research studies, does not form complex compounds there between. Thus, the qualitative combination of two drugs selected according to certain properties and selected from a certain group and according to a specific ratio between a polymer and the drugs impacts the functioning of the present composition.

Applicants respectfully submit that rejections based on obviousness cannot be sustained by mere conclusory statements. Instead, "there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 78 USPQ2d 1329, 1337 (Fed. Cir. 2006). Accordingly, Applicants submit that the Examiner has failed to establish a *prima facie* case that one skilled in the art would have been motivated to modify the compositions taught by the references to arrive at the presently claimed invention, when the references focus on the effectiveness of rifabutin alone, or in combination with isoniazid in the treatment of mouse tuberculosis, the ratio of rifabutin to isoniazid when used in combination is 1:2.5, the total drug to polymer ratio to be used is 1:3, and the average diameter of the microcapsules to be in the range of 0.5-400 μm.

In view of the above remarks, and when the claims are viewed in light of the specification, claim 1 is patentable over the cited references. Claims 5 and 6 are also patentable, at least by virtue of their dependence from claim 1. Accordingly, Applicants respectfully request reconsideration and withdrawal of the § 103(a) rejections of claims 1, 5 and 6.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

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Respectfully submitted,

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